

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

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| Applicant's or agent's file reference P 03/117-bz/gs | FOR FURTHER ACTION | see Form PCT/ISA/220 as well as, where applicable, item 5 below. |
| International application No. PCT/EP2004/006943 | International filing date (day/month/year) 25/06/2004 | (Earliest) Priority Date (day/month/year) 26/06/2003 |
| Applicant MERCK PATENT GMBH | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. Certain claims were found unsearchable (See Box II).

3. Unity of invention is lacking (see Box III).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

as suggested by the applicant.

as selected by this Authority, because the applicant failed to suggest a figure.

as selected by this Authority, because this figure better characterizes the invention.

b. none of the figures is to be published with the abstract.

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International application No.

PCT/EP2004/006943

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. type of material
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material
 - in written format
 - in computer readable form
 - c. time of filing/furnishing
 - contained in the international application as filed
 - filed together with the international application in computer readable form
 - furnished subsequently to this Authority for the purpose of search
2. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

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| International Application No PCT/EP2004/006943 |
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| A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07K14/815 A61K38/58 |
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| According to International Patent Classification (IPC) or to both national classification and IPC |
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| B. FIELDS SEARCHED |
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| Minimum documentation searched (classification system followed by classification symbols) |
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| IPC 7 C07K A61K |
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| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched |
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| Electronic data base consulted during the International search (name of data base and, where practical, search terms used) |
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| EPO-Internal, BIOSIS, WPI Data, PAJ |
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| C. DOCUMENTS CONSIDERED TO BE RELEVANT |
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| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|-----------------------|
| X ① | US 6 028 170 A (KU ET AL) 22 February 2000 (2000-02-22) "Analogs of hirudin" abstract column 2, line 13 – line 67 ----- -/- | 1-8 |

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| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. |
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| <input checked="" type="checkbox"/> Patent family members are listed in annex. |
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* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

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| Date of the actual completion of the international search |
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| 4 July 2005 |
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| Date of mailing of the international search report |
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| 11.08.2005 |
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| Name and mailing address of the ISA |
|-------------------------------------|

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|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 |
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| Authorized officer |
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| Niebuhr-Ebel, K |
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International Application No
PCT/EP2004/006943

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| A ② | MURAMATSU RYO ET AL: "Existence of beta-methylnorleucine in recombinant hirudin produced by <i>Escherichia coli</i> ." <i>JOURNAL OF BIOTECHNOLOGY</i> . 14 FEB 2002, vol. 93, no. 2, 14 February 2002 (2002-02-14), pages 131-142, XP002334171 ISSN: 0168-1656 abstract page 135, left-hand column, last paragraph - right-hand column, paragraph 1 page 140, right-hand column, last paragraph ----- | 1-8 |
| A ③ | BRAUN P J ET AL: "Use of site-directed mutagenesis to investigate the basis for the specificity of hirudin." <i>BIOCHEMISTRY</i> . 23 AUG 1988, vol. 27, no. 17, 23 August 1988 (1988-08-23), pages 6517-6522, XP002325668 ISSN: 0006-2960 abstract figure 1 table 1 ----- | 1-8 |
| A ④ | DODT J ET AL: "Interaction of site specific hirudin variants with alpha-thrombin." <i>FEBS LETTERS</i> . 29 FEB 1988, vol. 229, no. 1, 29 February 1988 (1988-02-29), pages 87-90, XP001206241 ISSN: 0014-5793 abstract page 88, left-hand column, last paragraph - right-hand column, paragraph 1 table 1 ----- | 1-8 |
| A ⑤ | KRSTENANSKY J L ET AL: "ANTICOAGULANT PEPTIDES NATURE OF THE INTERACTION OF THE CARBOXYL-TERMINAL REGION OF HIRUDIN WITH NONCATALYTIC BINDING SITE ON THROMBIN" <i>JOURNAL OF MEDICINAL CHEMISTRY</i> , vol. 30, no. 9, 1987, pages 1688-1691, XP002325669 ISSN: 0022-2623 abstract table III ----- | 1-8 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/006943

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|--|------------------|-------------------------|------------|------------------|
| US 6028170 | A 22-02-2000 | US | 5837808 A | 17-11-1998 |
| | | AU | 7721594 A | 27-03-1995 |
| | | WO | 9507295 A1 | 16-03-1995 |
| | | WO | 9304082 A1 | 04-03-1993 |

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1, 2, 7, 8 in part and 3-6 completely

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-8 (partially)

A modified hirudin molecule having a substitution L → T at position 13 and a pharmaceutical composition comprising said molecule.

Inventions 2-6: claims 1-8 (partially)

Modified hirudin molecules having a substitution L → T, A, H, Q or T at position 15 and a pharmaceutical composition comprising such a molecule.

Inventions 7-14: claims 1-8 (partially)

Modified hirudin molecules having a substitution V → A, G, H, K, N, P, Q or R at position 21 and a pharmaceutical composition comprising such a molecule.

Inventions (further): claims 1-8 (in part)

Modified hirudin molecules having a substitution at position 29, 30, 40, 47, 48, 53, or 57 and a pharmaceutical composition comprising said molecule.

Inventions (further): claims 1-8 (in part)

All combinations of modifications at more than one position as referred to in claim 1 and a pharmaceutical composition comprising such a molecule.

Inventions (further): claims 9 and 10

A peptide molecule as mentioned in claim 9 and its use for the manufacture of a modified hirudin molecule.
